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Repeat adverse drug reactions causing hospitalization in older Australians: a population-based longitudinal study 1980–2003

Min Zhang, C. D'Arcy J. Holman, David B. Preen & Kate Brameld[1]

School of Population Health, The University of Western Australia and [1]Genomics Directorate, Department of Health, Perth Business Centre, Perth, Australia

What is already known about this subject

- Adverse drug reactions (ADRs) are a major cause of morbidity in older patients and represent a major burden on healthcare.
- The rate of ADR-related hospital stays in older people in Western Australia (WA) increased fivefold from 1981 to 2002.
- Little information is available regarding repeated ADRs in the elderly and the drugs most responsible.

What this study adds

- Repeat ADR-related hospitalizations have consistently increased faster than first-time ADRs in the elderly in WA from 1980 and had reached 30.3% of all ADRs by 2003.
- The mean time interval declined with each successive repeat ADR and the most common repeat ADRs were nausea and vomiting, haemorrhage due to anticoagulants, drug-induce osteoporosis and poisoning by cardiovascular agents.
- Strategies to ensure the safer use cardiovascular agents, corticoids, nonsteroidal anti-inflammatory drugs, opioids and, in particular, anticoagulants, in this population are warranted.

Correspondence
Dr Min Zhang, School of Population Health, The University of Western Australia, 35 Stirling Highway, Crawley, Perth, WA 6009, Australia.
Tel.: +61 8 6488 8175
Fax: +61 8 6488 1188
E-mail: min.zhang@uwa.edu.au

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Aim
To examine trends in the rate of repeat adverse drug reactions (ADRs) causing hospitalization in older Australians and to identify the most common ADRs and drugs most often implicated in repeat and first-time ADRs.

Methods
Analysis of routinely collected hospital record administrative data, with International Classification of Diseases external cause codes for ADRs extracted from the Western Australia (WA) Hospital Morbidity Data System and WA Death Register, for people aged ≥60 years in 1980–2003.

Results
A total of 37 296 people aged ≥60 years with an ADR-related hospitalization were identified. Among them, 6853 (18.4%) patients had 10 212 repeat ADRs. Repeat ADRs consistently increased from 1980 and reached 30.3% of all ADRs by 2003. The mean time interval declined with each successive repeat ADR (810, 606 and 299 days for the first, second and higher ranked repeat episodes, respectively). The most common repeat ADRs were nausea/vomiting (8.0%), haemorrhage due to anticoagulants (5.5%), drug-induced osteoporosis (4.8%) and poisoning by cardiovascular agents (3.9%). The drugs most often involved in repeat ADRs were cardiovascular agents (15.6%), antineoplastic drugs (11.0%), corticoids (10.1%), anticoagulants (8.6%), antirheumatics/nonsteroidal anti-inflammatory drugs (5.1%) and opioids (4.9%). The trends of anticoagulants and antineoplastic drugs implicated in repeat ADRs were still rising at the end of the study. The specific drug classes involved in repeat ADRs differed in relative importance from first-time ADRs.

Conclusions
Repeat ADR-related hospitalizations have consistently increased in elderly Australians from 1980 to 2003. Strategies to ensure the safer use of medicines, in particular anticoagulants, in this population are warranted.

Introduction

Adverse drug reactions (ADRs) are a major cause of morbidity in older patients and represent a major burden on healthcare [1–3]. In western countries, ADRs cause 3–6% of all hospital admissions [1, 4] and are responsible for approximately 5–10% of inpatient costs [5–7]. Dawes found that the rate of ADR-related hospital stays in people aged ≥70 years in Western Australia (WA) doubled between 1980 and 1991, with the main classes of drugs responsible being cardiovascular agents, antirheumatics and cytotoxics [8]. Further, Burgess and colleagues have reported more recently that the rate of ADRs associated with hospitalizations in people aged ≥60 years more than doubled between 1991 and 2002, with the most frequent classes of drugs being anticoagulants, cytotoxics and antirheumatics, including nonsteroidal anti-inflammatory drugs (NSAIDs) [9].

Older patients are particularly vulnerable to ADRs because of multiple-drug regimens and age-associated changes in pharmacokinetics and pharmacodynamics [10, 11]. Despite the magnitude of the problem, studies in this segment of the population have often been inadequate. There are few studies that have examined repeat ADRs in the elderly. Little information is available regarding the trends over time in repeated ADRs and the drugs most likely to be responsible. The aims of the present study were: (i) to examine trends over time in the rate of repeat ADR-related hospitalizations in the elderly WA population; (ii) to describe the most common ADRs observed; and (iii) to identify the drugs most often implicated in repeat ADRs and if these differ from those causing first-time ADRs.

Methods

An extract of the WA Hospital Morbidity Data System (HMDS) was used for this study. The WA HMDS is a state-wide, population-based statutory register held at the WA Department of Health. The extract was prepared under an encryption procedure to protect the identity of individual patients and the de-identified data were provided in February 2005. These administrative data comprised all separations (transfers and discharges) of inpatients separated from all WA public and private hospitals. Hospital separations were coded according to the International Classification of Diseases (ICD) ninth revision (ICD-9) (1981–1987) [12], ICD-9-CM (January 1988 to June 1999) [13] or lCD-10-AM (July 1999 to December 2003) [14]. The performance of the linked data system has been assessed by comparison with clerical investigation, the results of which estimated both the proportions of invalid links (false-positives) and missed links (false-negatives) to be 0.11% [15]. Death records were also extracted from the WA Death Registry for all subjects in the study who died prior to 31 December 2003. Census and intercensal WA population estimates for 1980–2003 by sex and 10-year age group were obtained from the Australian Bureau of Statistics. The average annual population in WA between 1980 and 2003 was 1.63 million, including 224 000 people aged ≥60 years. The data presented here are based on records of inpatients who both resided and were treated in WA. The project was approved by the Human Research Ethics Committee of The University of Western Australia.

An ADR was defined as any hospital separation with an ICD code of E930–E949 (ICD-9 and ICD-9-CM) or Y40–Y59 (ICD-10-AM), which were additional codes used to indicate an 'external cause' relevant to drug use, grouped into 20 broad categories. The codes included any adverse effect caused by correct drug use, medicaments or biological substances properly administered in therapeutic or prophylactic dosages, excluding therapeutic failures, intentional and accidental poisoning, and abuse. Thus, the definition of ADRs used in the study was consistent with that of the World Health Organization, as a 'response to a medicine that is noxious and unintended, and that occurs at doses normally used in humans' [16]. ADRs were assessed and recorded by senior hospital medical officers, who translated the doctors' text into ICD codes. The study included all ADRs that resulted in hospital admission or occurred while patients were in hospital and extended the length of hospital stay. An ADR episode was defined as a period of continuous treatment for an ADR in one or more hospitals, as a person admitted to one hospital might have been transferred to another before they were discharged. All records were checked for interhospital transfers and, where these were evident, the information was concatenated into a single 'episode' for analysis.

All WA residents aged ≥60 years with a hospital episode for an ADR in 1980–2003 were included in the study. However, to ensure correct identification of first-time episodes, we initially examined all hospitalizations dating back to 1970. The total data extract included over 800 000 hospital separations and these records were audited to ensure each patient fitted the selection criteria. Non-WA residents were excluded. Each patient's first ADR record was identified, thereby distinguishing 'first-time' from 'repeat' episodes. There were 380 (1.0%) patients aged ≥60 years whose first ADR episode occurred prior to 1980 and were included in the analysis. A total of 47 508 ADR episodes in 37 296 patients remained for analysis.

Statistical analysis was performed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA). Age-standardized

hospital morbidity rates were calculated using direct standardization, with the 2001 WA census population as the standard weights. The rates of repeat ADRs were plotted from 1980 to 2003. ADR records were classified by sex, 10-year age group and drug category. The difference of rate, proportion and time interval between subgroups was compared using a *t*-test. The frequency and distribution of the most common ADRs and drugs responsible for repeat and first-time ADRs were also examined. If multiple drugs were thought to be responsible for an ADR, only the primary drug was included in the study.

Results

A total of 37 296 subjects aged ≥60 years with a first-time hospital episode for an ADR in 1980–2003 were included in the study. The mean (± SD) length of follow-up for study subjects was 4.2 ± 4.3 years. The study sample comprised 16 361 (43.9%) men and 20 935 (56.1%) women (Table 1). Most (95.6%) of patients had comorbid conditions and 6853 (18.4%) patients had repeat hospital episodes related to ADRs, accounting for 10 212 separate hospital episodes. The mean time interval (95% confidence interval) between ADR episodes declined with each successive repeat ADR, and were 810.2 (785.9, 834.5), 606.4 (567.1, 645.7) and 298.7 (271.1, 326.3) days for the first, second, and third or more repeat ADRs, respectively. The differences in mean time interval between ADR episodes decreased significantly ($P < 0.001$) with frequency. By the end of the study period, 22 721 (60.9%) patients had died, although only 10 deaths (0.04%) were ascribed to an ADR. The crude cumulative mortality proportions were 68.1% and 59.3% in the patients with and without, respectively, repeat ADRs at significantly different levels ($P < 0.001$).

Figure 1 shows trends in age-standardized hospital morbidity rates of first-time and repeat ADRs in people aged ≥60 years in WA. The rate of repeat ADRs consistently increased from 1980 and had reached 30.3% of all ADRs by 2003. Figure 2 shows trends in age-standardized hospital morbidity rates of repeat ADRs by age group. The rates increased with age, with the largest increases occurring in those aged ≥80 years. By 2003 the rates of ADR were 9.7, 5.2 and 3.0 per 1000 person-years for those aged ≥80, 70–79 and 60–69 years, respectively. The rate in people aged ≥80 years in 2003 was significantly different ($P < 0.01$) from that in those aged <80 years. There was no statistical difference in the rates between men and women, although the rate was higher in women (5.5 per 1000 person-years) than that in men (4.4 per 1000 person-years) in 2003.

Table 1
Characteristics of subjects aged ≥60 years with an adverse drug reaction (ADR) causing hospitalization, WA 1980–2003

Characteristic	Subjects ($N = 37296$)	Frequency (%)
Age at first ADR (years)		
<65	5067	13.6
65–69	5813	15.6
70–74	7188	19.3
75–79	7495	20.1
≥80	11 733	31.5
Calendar period of first ADR (years)		
1980–1984	2280	6.1
1985–1989	3999	10.7
1990–1994	6995	18.0
1995–1999	11 356	30.4
2000–2003	12 966	34.8
Gender		
Male	16 361	43.9
Female	20 935	56.1
Race		
Non-Aboriginal or TSI	36 954	99.1
Aboriginal and/or TSI	342	0.9
Residential location		
Metropolitan	30 900	82.9
Regional	6396	17.1
Hospital of first ADR admission		
Public	29 536	79.2
Private	7022	18.8
Missing	738	2.0
No. of comorbidity		
0	1657	4.4
1–3	12 619	33.9
4–6	12 381	33.2
≥7	10 639	28.5
Repeat ADRs		
No	30 443	81.6
Yes	6853	18.4
Survival status at the end of the study		
Alive	14 575	39.1
Dead	22 721	60.9

TSI, Torres Strait Islander.

Table 2 reports the most common ADRs in first-time and repeat hospital episodes in those aged ≥60 years in 1980–2003. The most common ADRs were nausea and vomiting (8.0%), haemorrhagic disorder due to circulating anticoagulants (5.5%), drug-induce osteoporosis (4.8%) and poisoning by cardiovascular agents (3.9%) for repeat hospital episodes. In comparison, the most common diagnoses for first-time ADR hospital episodes

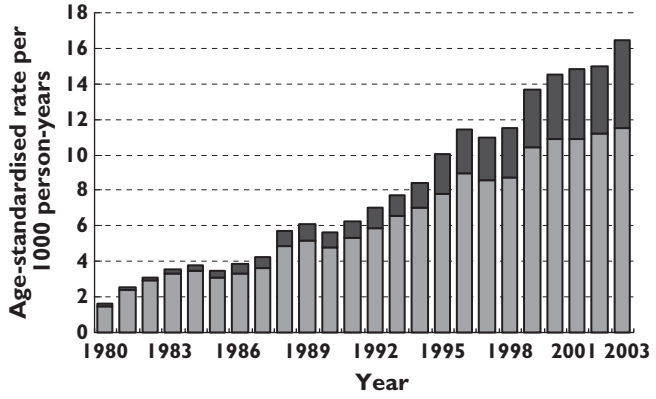

Figure 1
Trends in age-standardized hospital morbidity rates of first-time (▢) and repeat (■) adverse drug reactions (ADRs) in people aged ≥60 years, WA 1980–2003

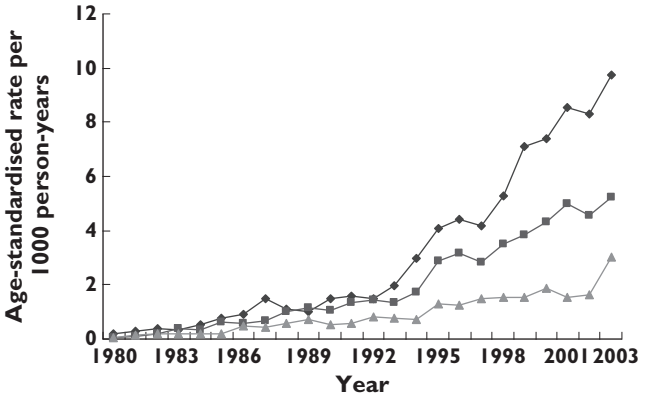

Figure 2
Trends in age-standardized hospital morbidity rates of repeat adverse drug reactions in people aged ≥60 years by age group, WA 1980–2003. 80+ years (—◆—), 70–79 years (—■—), 60–69 years (—▲—)

Table 2
Distribution of the most common adverse drug reactions (ADRs) observed in first-time and repeat hospital episodes in people aged ≥60 years, WA 1980–2003

ICD code	ADR diagnosis	First-time episodes (*N* = 37 296) *n*	%	Repeat episodes (*N* = 10 212) *n*	%
787.0–787.03/R11	Nausea and/or vomiting	2819	7.6	816	8.0
286.5/D68.3	Haemorrhagic disorder due to circulating anticoagulants	1474	4.0	557	5.5
733.09/M81.4	Drug-induce osteoporosis	280	0.8	495	4.8
972.0–972.9/T46.0-T46.9	Poisoning by agents of cardiovascular system	1828	4.9	397	3.9
693.0/L27.0–L27.1	Dermatitis due to drugs	1727	4.6	355	3.5
288.0/D70	Drug-induce agranulocytosis	935	2.5	331	3.2
I95.2	Hypotension due to drugs	1054	2.8	300	2.9
284.8/D61.1	Drug-induce aplastic anaemia	301	0.8	196	1.9
558.2/K52.1	Unspecified adverse effect of drug or medicament	390	1.0	151	1.5
966.0–968.9/T42.0–T42.8	Poisoning by anticonvulsants and anti-Parkinsonism	504	1.4	113	1.1
Total		11 312	30.3	3711	36.3

were nausea and vomiting (7.6%), poisoning by cardiovascular agents (4.9%), dermatitis due to drugs (4.6%) and haemorrhagic disorder due to circulating anticoagulants (4.0%).

The overall distribution of the 20 broad drug categories responsible for repeat ADRs, compared with that for first-time ADRs, is shown in Table 3. We found that 5696 repeated ADRs (55.8%) involved drug classes different from those implicated in first-time ADRs. The other 4516 repeated ADRs (44.2%) involved the same drug class as those responsible for first-time ADRs. The most common drug categories responsible for repeat ADRs were cardiovascular (15.6%) and analgesics/NSAIDs (14.7%). These results were similar to those for first-time ADRs. When analysing the more specific drug classes involved in repeat ADRs, at the four-digit E-code level (ICD-9 and ICD-9-CM) and three-digit level for Y-code (ICD-10-AM), differences occurred in comparison with first-time ADRs. The most often implicated agents for repeat ADRs were antineoplastic/immunosuppressive drugs (11.0%), corticoids/synthetic analogues (10.1%), anticoagulants (8.6%),

Table 3
Distribution of drug categories responsible for first-time and repeat adverse drug reaction (ADR) hospital episodes in people aged ≥60 years, WA 1980–2003

ICD code	Drug category	First-time ADRs No	First-time ADRs %	Repeat ADRs No	Repeat ADRs %
E942/Y52	Agents primarily affecting cardiovascular system	6 693	17.9	1 590	15.6
E935/Y45	Analgesics/antipyretics/anti-inflammatory drugs*	6 481	17.4	1 502	14.7
E932/Y42	Hormones (including synthetic, antagonists)	2 705	7.3	1 358	13.3
E933/Y43	Primarily systemic agents†	2 744	7.4	1 158	11.3
E934/Y44	Agents primarily affecting blood constituents	3 474	9.3	977	9.6
E944/Y54	Agents affecting water/mineral balance/uric acid	2 841	7.6	746	7.3
E930/Y40	Systemic antibiotics	3 475	9.3	726	7.1
E939/Y49	Psychotropic drugs	2 166	5.8	593	5.8
E936/Y46	Antiepileptics/anti-Parkinsonism drugs	1 362	3.7	403	3.9
E947/Y57	Other and unspecified medicaments	1 213	3.3	306	3.0
E941/Y51	Drugs affecting autonomic nervous system	1 239	3.3	303	3.0
E931/Y41	Other systemic anti-infectives/antiparasitics	528	1.4	133	1.3
E946/Y56	Topical agents affecting skin, ENT, dental	631	1.7	119	1.2
E945/Y55	Agents affecting muscle/respiratory system	388	1.0	85	0.8
E943/Y53	Agents primarily affecting gastrointestinal system	329	0.9	77	0.8
E937/Y47	Sedatives, hypnotics, antianxiety drugs	342	0.9	74	0.7
E938/Y48	Anaesthetics, therapeutic gases	555	1.5	37	0.4
E949/Y59	Other vaccines/biologicals	77	0.2	15	0.1
E940/Y50	CNS stimulants	31	0.1	5	<0.1
E948/Y58	Bacterial vaccines	22	0.1	5	<0.1
Total		37 296	100.0	10 212	100.0

**Including nonsteroidal anti-inflammatory agents.*
†Including inter alia*, antineoplastics and immunosuppressives.*

antirheumatics/NSAIDs (5.1%) and opioids/related analgesics (4.9%), which accounted for 39.7% of all drugs responsible. In contrast, the most commonly responsible drugs for first-time ADRs were anticoagulants (7.8%) and antirheumatics/NSAIDs (7.2%).

The frequency of the five drugs most involved in first-time and repeat ADR hospital episodes from 1980 to 2003 are shown in Figures 3 and 4. The time trends observed for repeat ADRs were similar to those for first-time ADRs. Antineoplastic/immunosuppressive drugs and anticoagulants were still rising at the end of the study, whereas corticoids/synthetic analogues and opioids peaked in 1998 and 2001, respectively, similar to the trends observed in first-time ADRs.

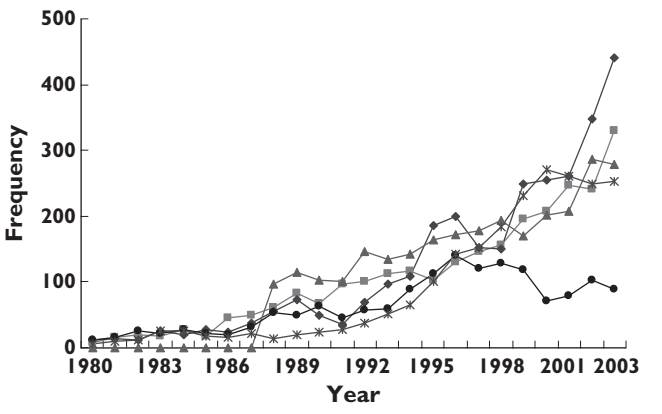

Figure 3
Annual frequency of the five drug classes most often implicated in first-time adverse drug reaction hospital episodes in people aged ≥60 years, WA 1980–2003. Antineoplastics/immunosuppressives (—■—), anticoagulants (—◆—), antirheumatics/NSAIDs (—▲—), corticoids/synthetic analogues (—●—), opioids/related analgesics (—✳—)

Discussion

This study examined repeat ADRs causing hospitalization in older people in the WA population. Our data provide information, not readily available elsewhere,

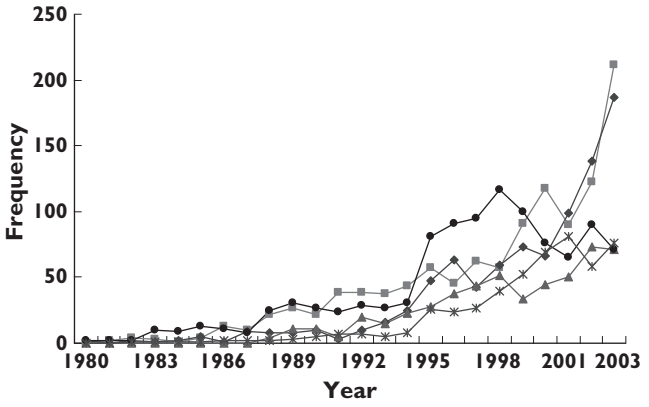

Figure 4

Annual frequency of the five drug classes most often implicated in repeat adverse drug reaction hospital episodes in people aged ≥60 years, WA 1980–2003. Antineoplastics/immunosuppressives (—■—), anticoagulants (—◆—), antirheumatics/NSAIDs (—▲—), corticoids/synthetic analogues (—●—), opioids/related analgesics (—✳—)

that repeat ADRs have consistently increased at a greater rate than first-time ADRs in older Australians since 1980, and had reached 30.3% of all ADRs by 2003. There was a relationship between the rank order of repeat ADRs and the mean time interval between each pair of ADR episodes. The results from this study suggest that older people, who experienced an ADR, were more susceptible to repeat ADR-related hospitalization. Few studies have investigated the relationship between first-time and repeat ADR-related hospitalizations. Of the few that have, one study, using a survey conducted in an internal medicine department, reported that the presence of ADRs was similar in first admissions and readmissions [17]. This prospective cohort study was limited by small sample size ($n = 630$ patients) and a relatively short period of follow-up (18 months). The present study followed 37 296 patients with first-time ADRs for up to 24 years.

Other strengths of our study include the retrospective cohort design using population-based routinely collected and audited data of high quality [15], which overcomes issues related to selection and recall bias as well as lower response and loss of follow-up. The advantages of our study over earlier work include the analysis of data at the individual patient level. This allowed us to follow up hospital separation records individually and identify repeat ADRs in the same patient regardless of changes in the treating hospital. The limitations of the study should also be considered when interpreting our findings. An important limitation was the lack of detailed specification in the particular drug responsible for ADR-related hospital admission available from ICD codes. Only very broad groupings of drugs were available (e.g. antineoplastics and immunosuppressives are grouped together under code E933). As with other studies of this nature, reliability of ascertainment may vary because the presence of an ADR is subject to clinical judgement. Further, the study focused only on ADRs resulting in hospitalization, which either caused hospital admission or extended hospital stay, whereas most ADRs (90%) are fairly minor and occur in the community [18]. However, ADRs resulting in hospitalization represent the more serious side-effects of medication use and lead to significant morbidity and financial costs. They are thus a particularly appropriate object of analysis. Another potential limitation is that loss to follow-up may have occurred as a result of interstate migration. However, the rate of population turnover was only 3.5% in WA residents during the study period [19]. The fact that death records were linked to 60.9% of study subjects also indicated a high level of follow-up in the study.

As the study was longitudinal, the influence of factors that changed with time should be considered. The results are consistent with an increase in drug exposure in elderly Australians, believed to be an increase of 4.7% over 2000–2001 [20]. This increase exceeded population growth, suggesting either a larger population at risk or a higher average level of drug exposure per patient. Our results, derived from the population-level data, suggest a strong correlation of repeat ADRs with changes in medication use in the community [9, 21]. Efforts to improve coding and the increase in the number of hospital admissions during the observation period may have contributed to some of the observed rise in ADRs. However, a validation study by Dawes involving a review of 377 hospital charts found there was a real increase in hospital morbidity caused by ADRs from 1980 to 1991 in WA [8].

Several studies have found that ADRs are becoming a major problem in older people in Australia [8, 9]. A meta-analysis of 68 observational studies reported that ADR-related hospitalizations in the elderly were four times higher than in younger people [22]. Advancing age is also associated with both increased morbidity and polypharmacy [10, 11]. Older patients are, consequently, more prone to developing ADRs. Fewer older adults are included in pharmacological trials, which examine the efficacy and safety of drugs. However, some studies have reported that age was not an independent risk factor of adverse drug reactions [23]. Several studies have found that a major risk factor for ADRs in elderly populations was inappropriate drug use [3, 24, 25]. More than 75% of ADRs leading to hospitalization are related to

known pharmacological properties (type A), which are dose-related, thus these are usually predictable and potentially avoidable [2]. Type A ADRs are more common in the elderly [26]. Therefore, the risk of side-effects must be balanced against the benefits to older patients of the increased use of powerful pharmaceutical agents in treating diseases.

This study provides information on the most common ADRs and the drug classes most often implicated in repeat ADRs contrasted with first-time ADRs. Although differences between first-time and repeat ADRs were identified, there were also similarities found in both types of ADR. The most common ADRs were nausea and vomiting, haemorrhage due to anticoagulants and poisoning by cardiovascular agents in both repeat and first-time ADRs. The most common drugs responsible for repeat and first-time ADRs were cardiovascular drugs. Antineoplastic drugs, corticoids/synthetic analogues, anticoagulants, antirheumatics/NSAIDs, opioids/related analgesics and systemic antibiotics were commonly found in both repeat and first-time ADRs, although their ranking differed. The trends for the five drug classes most often involved in repeat ADRs were similar to those observed for first-time ADRs. ADRs due to antineoplastic/immunosuppressive drugs and anticoagulants were still rising at the end of the study, whereas corticoids/synthetic analogues and opioids peaked in 1998 and 2001, respectively, following the trends observed in first-time ADRs. The rise of antineoplastic drugs involved with repeat ADRs was expected because of an increase in the number of antineoplastic drugs in use and the increase in the prevalence of cancer in the WA population due to longer survival of patients with active disease [27].

The results of our study highlight the role of anticoagulants in both first-time and repeat ADRs. Consequently, a considerable proportion of ADRs resulting in hospitalizations may be preventable by improved laboratory monitoring of anticoagulant use. ADRs related to anticoagulants have undergone the greatest increase in the past decade to become the most common and the second most common drug class implicated in first-time and repeat ADRs, respectively, in 2003. The sharp rise in anticoagulants responsible for repeat ADRs in the elderly in WA is of great concern. Many substances interact adversely with anticoagulants. Older adults are more susceptible to these interactions, and also have a higher risk of haemorrhage. Special attention to the rational and safer use of anticoagulants is warranted, which include lower anticoagulant doses and careful laboratory monitoring. In addition, the increasing use of alternative or complementary therapies raises the potential for adverse interactions with anticoagulants [28].

In conclusion, repeat ADRs causing hospitalization have consistently increased faster than first-time ADRs in the elderly in WA from 1980 and had reached 30.3% of all ADRs by 2003. The mean time interval between ADRs declined with each successive repeat ADR. The most common ADRs were nausea and vomiting, haemorrhage due to anticoagulants and poisoning by cardiovascular agents in both repeat and first-time ADRs. Our results suggest that greater care in setting the doses of medication in the elderly is warranted, particularly in the case of anticoagulants.

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